

Palliative external beam radiotherapy for lung cancer patients with malignant airway obstruction

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Research

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Abstract

Background Significant proportion of lung cancer patients suffer from malignant airway obstruction (MAO). Palliative external beam radiotherapy (EBRT) is often attempted to control symptoms caused by MAO. In this study, we report the effect of palliative EBRT on lung cancer with MAO and analyze the factors that influence it.

Methods This study included 75 patients with MAO in lung cancer who underwent palliative EBRT, between 2009 and 2018 and were analyzed retrospectively. Change of dyspnea, tumor response, and overall survival (OS) were recorded. Univariate and multivariate analyses were done to find the prognostic factors for treatment outcomes.

Results The median follow-up duration was 2.5 months, and the median OS was 2.3 months. Out of 75 patients, dyspnea was improved in 46 patients (61.3%), and tumor was partially decreased in 39 patients (52%). The symptom improvement was significantly affected by tumor response and radiation dose. The tumor response was significantly affected by disease status, radiation dose, and time to EBRT.

Conclusions Palliative EBRT is an effective and safe treatment option for patients with MAO in lung cancer. Especially, high-dose irradiation and prompt treatment can improve treatment results.

Background

Lung cancer is the most commonly diagnosed cancer worldwide and the most common cause of cancer-related death [1]. Although advances in imaging technology have made it possible to detect early-stage lung cancer, but most lung cancer patients are still diagnosed at an advanced stage [2]. In this late course of disease, bulky and progressed intrathoracic tumors can cause symptoms such as cough, hemoptysis, chest pain, superior vena cava syndrome, hoarseness, or dyspnea from malignant airway obstruction (MAO) [3].

For MAO, a third of lung cancer patients are obstructed at diagnosis, and a significant proportion of the other patients will develop obstruction at some point in the course of the disease [4]. MAO can cause pneumonia as well as dyspnea, and can be an immediate cause of death, so if possible, it requires immediate treatment [5].

Various palliative-intent treatments are attempted to improve symptoms and penetrate blocked airways [4, 6]. External beam radiotherapy (EBRT) is a preferred treatment option for MAO because it is non-invasive, safe, and simpler than other methods such as a bronchoscopic procedure, laser ablation, and intraluminal brachytherapy [7, 8]. However, there are several limitations in EBRT in that there is no standardized guideline (radiation dose, fractionation, and time for EBRT) and the result data are insufficient.

Therefore, in this study, we report our institutional experience and treatment outcomes of treating lung cancer patients with MAO by palliative EBRT. We analyze how treatment by EBRT is better for symptom relief, good tumor response, and survival.

Methods

Patient selection

For this study, the inclusion criteria were as follows: 1) patients with histologically proven primary lung cancer, 2) patients suffering from dyspnea with a radiographic finding of MAO on chest X-ray or computed tomography (CT), and 3) patients treated by palliative-intent EBRT for the obstructive pulmonary mass. Patients who received prior systemic chemotherapy were included in this analysis. In contrast, patients who had any of following conditions were excluded from this study: 1) no follow-up image data for showing the treatment response, 2) no follow-up medical records for showing the change of symptoms, and 3) a previous history of RT and surgery at chest. Among those patients who received palliative EBRT at Gyeongsang National University Hospital (GNUH) and Gyeongsang National University Changwon Hospital (GNUCH) between November 2009 and December 2018, we selected 75 patients who fully fulfilled the above criteria for analysis and retrospectively reviewed their medical charts, treatment records, and the results of image work-up.

This study was retrospective, with no informed consent from individual patients, but was done in accordance with relevant guideline; the study protocol was approved by the Institutional Review Boards (IRBs) at GNUH (IRB No. GNUH 2020-03-009) and GNUCH (IRB No. GNUCH 2020-03-020).

Radiotherapy

For radiotherapy (RT), all patients were immobilized in the supine position and had received CT simulations. The scanned images were imported into the Eclipse treatment-planning system. Total or partial lung mass including conglomerated metastatic lymph nodes presumed by clinicians to induce airway obstruction was delineated as gross tumor volume. The clinical target volume was not delineated, because treatment was delivered with palliative intent. Subsequently, a volumetric margin of 10 mm was applied to make the planning target volume (PTV). Three-dimensional conformal RT plans were created and used to prescribe a median dose of 39 Gy (range, 24–59 Gy), 2–3 Gy per fraction, equal to a median equivalent dose in 2 Gy per fraction (EQD2) 42.2 Gy (range, 26–62.2 Gy). All plans were normalized so that 100% of PTV received more than 90% of the prescribed dose.

If the changes in atelectasis or airway position were observed by means of daily chest x-rays during RT, the previous procedure was repeated from CT scanning to RT planning. We then continued with the remaining RT with the new RT plan.

Statistical analysis

The severity of dyspnea was recorded by radiation oncologists based on the American Thoracic Society (ATS) score, and the differences in score before, during, and after RT was used to assess symptom improvement [9]. We defined time for EBRT as the period from the day of dyspnea with an ATS score of 2 or higher to the day of RT start. In simulated chest CT images, the degree of obstruction, presence of carina involvement, and length of the tumor blocking the airway were measured. On mean 27 days (range, 4–90 days) after the end of RT, all patients had scanned chest CT for treatment response evaluation. Tumor response was divided into complete response (CR), partial response (PR), progressive disease (PD), and stable disease (SD) according to the Response Evaluation Criteria In Solid Tumors (RECIST) criteria, and we defined CR or PR in the RT field area as the responding group [10]. Acute toxicity was evaluated by National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 [11].

Simple and multivariate logistic regression analyses were done to identify prognostic factors of symptom relief and tumor response. The overall survival duration was defined as the period from the date of end of RT to the date of any death. Kaplan-Meier method and Log-rank test were used for survival curves. All analyses were done using the SPSS program, and a p value < 0.05 was considered statistically significant.

Results

Patient characteristics

Patient characteristics are summarized in Table 1. For the total of 75 patients (GNUH, 48 patients; GNUCH, 27 patients) enrolled in this study, their median age was 68 (range, 49–84 years) and most were male (80%). Their Eastern Cooperative Oncology Group (ECOG) performance scores were 0 (1 patients), 1 (37 patients), 2 (22 patients), and 3 (15 patients). The histology was small-cell lung cancer in 23 (30.7%) patients and non-small-cell lung cancer in 52 (69.3%) patients: squamous cell carcinoma, 37 patients; and adenocarcinoma, 15 patients. At the time of complaint of dyspnea, 51 (68%) patients had lung cancer with relapse or refractory disease status after palliative chemotherapy; the other 24 (32%) patients had untreated, just-diagnosed lung cancer. Most of the patients (92.5%) did not receive chemotherapy during the course of RT. In initial chest CT, the degree of obstruction was partial in 56 (74.7%) patients and total in 19 (25.3%). The number of carina-involved patients was 37 (49.3%) out of 75 patients. All of the patients with total obstruction had carina involvement. The mean length of the tumor blocking the airway was 5.6 cm (range, 3.2–9.7 cm). The patients' dyspnea level before RT was divided into 2, 3, and 4 points based on ATS score, for 9, 32, and 34 patients, respectively. Time for EBRT was mean 24 days (range, 1–112 days).

Treatment outcomes

The median follow-up duration was 2.5 months (range, 0.2–32.2 months), and 71 patients (94.7%) died at the end of the follow-up period. The median overall survival (OS) was 2.3 months, and 1-year OS rate was 8%. The degree of symptomatic change in dyspnea was divided based on the difference in ATS scores before and after RT, as shown in Table 2. According to the ATS score gap, the number of patients with 3, 2, and 1 was 8 (10.7%), 18 (24%), and 20 (26.7%), respectively. In 46 patients (61.3%), the symptoms of dyspnea improved, although there was a difference in degree. On the other hand, 24 patients (32%) had no change in symptoms, and 5 patients (6.7%) had worsened symptoms despite treatment. Tumor response was classified into CR, PR, SD, and PD and the number of patients was 0 (0%), 39 (52%), 29 (36%), and 7 (9.3%), respectively. A total of 52% of patients showed a tumor response after RT. The tumor response in one patient who underwent Palliative EBRT is shown in Figure 1 by comparing chest CT images before and after treatment. Based on CTCAE criteria, acute toxicity was grade 1 esophagitis in 21 patients, grade 2 esophagitis in 10 patients, and grade 1 radiation dermatitis in 3 patients. No patient suffered from grade 3 or higher toxicity.

Prognostic factors

We used logistic regression analyses to find factors that could affect the treatment outcomes. In the univariate analysis, ECOG performance status ($p = 0.003$), disease status ($p = 0.007$), degree of obstruction ($p = 0.008$), tumor length ($p = 0.001$), EQD2 ($p = 0.007$), time to RT ($p = 0.002$), and tumor response ($p < 0.001$) were significant factors in symptom improvement. EQD2 ($p = 0.034$) and tumor response ($p = 0.001$) remained significant in the multivariate analysis. For tumor response, ECOG performance status ($p = 0.047$), pathology ($p = 0.036$), disease status ($p < 0.001$), degree of obstruction ($p = 0.034$), EQD2 ($p = 0.013$), and time to RT ($p = 0.001$) were statistically significant in univariate analysis. However, disease status ($p = 0.006$), EQD2 ($p = 0.024$), and time to RT ($p = 0.006$) remained significant in the multivariate analysis. These results for symptom improvement and tumor response are shown in Tables 3 and 4. The analysis results for the factors affecting the OS are shown in Figure 2. Patients with an ECOG performance status of 0–2 had a 1-yr OS rate of 10.1% and median OS of 4.3 months, whereas those with ECOG performance status 3 had a median OS of 0.2 months; this difference was statistically significant. For tumor response, 1-yr OS rate that was statistically significant differed by 14.5% in the responding group and 3.3% in the non-responding group.

Discussion

In this study, we analyzed the effects of palliative EBRT and its related factors in 75 patients with lung cancer with MAO. Median EQD2 42.2 Gy was irradiated, 61.3% of patients showed improvement of dyspnea, and 52% of patients showed partial tumor response. The tumor response was good in patients with untreated disease status, high-dose irradiation, or short time to RT. Symptom improvement was better in patients with good tumor response and high-dose irradiation (EQD2 \geq 42.2 Gy). The OS of all

patients was poor, but that was relatively high in patients with good performance status or good tumor response.

MAO is present in the late course of the disease in a large proportion of lung cancer patients. The prognosis of the patients is very poor and life expectancy is short. However, the symptoms, such as dyspnea, cough, or hemoptysis that accompany MAO, deteriorate the quality of life and require palliative treatment. It is difficult to define standard guidelines, because this treatment should be applied in a variety of ways depending on the patient's overall condition as well as on the severity of the patient's symptoms.

Among palliative treatment methods, EBRT has some advantages that can be easily applied. First, palliative EBRT is effective in lung cancer patients with MAO. Lee et al. [7] gave a median 30 Gy EBRT to 95 patients with airway obstruction in lung cancer. They defined responders as patients with improved chest x-rays or symptoms and reported a total response rate of 78.9%. They also reported that a higher response was observed in patient with a biologically effective dose ≥ 39 Gy or tumor length ≤ 6 cm. Another investigator, Nihei et al. [12], gave 30 Gy in 10 fractions EBRT to 24 patients with airway stenosis in non-small-cell lung cancer. They assessed treatment response by chest images and reported a response rate of 54.2%, which lasted for a median of 116 days, corresponding to about 66% of the patient's remaining survival. Our study showed a satisfactory therapeutic effects (symptom response, 61.3%; tumor response, 52%) similar to those of these previous studies. In addition, the effects may be improved by controlling factors such as high-dose irradiation and short time to RT. Second, palliative EBRT is noninvasive and safe in lung cancer patients with MAO. In MAO patients, therapeutic bronchoscopic procedures are often attempted for palliation. Ernst et al. [13] reported procedure-related toxicity in 554 patients who received therapeutic bronchoscopy at four hospitals. They reported that general anesthesia was needed in 65.3% of patients and adverse events, such as hypoxia, pneumothorax, escalation of care, bleeding, and hypotension, were found in 25% of patients with malignant tumors. Another study reported the side effects of therapeutic bronchoscopy in 15 institutions and 947 MAO patients [14]. They reported that side effects could differ depending on the institution and skill of the operator, and if side effects occur, more than 50% of patients develop additional severe adverse events, such as permanent disability or death. On the other hand, in previous studies with EBRT and in our study, grade 3 or higher acute toxicity was not observed in any patients. Although chronic toxicity has not been evaluated, late effects are often less concerning because of their short lifespan in most palliative therapy.

However, there are several disadvantages of palliative EBRT. First, it cannot immediately improve symptoms in MAO patients. Lee et al. [7] reported that median time for resolving the symptom or radiologic findings was 7 days after EBRT, and for Nihei et al. [12] it was 24 days. EBRT alone is not effective in patients with acute phases of respiratory distress or requiring dramatic and immediate symptomatic improvement. This shortcoming can be overcome by combining the bronchoscopic procedure with early effects and the EBRT with delayed effects. Combined treatment studies have reported good results in improving symptom-free survival and progression-free survival as well as symptom improvement [15, 16]. Second, palliative EBRT has a relatively long duration of treatment.

Because of the short survival of patients with MAO, a long time spent on treatment can be a disadvantage. To overcome this shortcoming, hypofractionated RT can be considered. Theoretically, the risk of late complications increases, but considering the short life expectancy, a faster tumor response can be expected. Additional studies are needed to find proper RT schedules that increase response rates and reduce treatment duration while maintaining low side effects.

The limitation of this study is its retrospective nature, where the patient characteristics and outcome data are not well controlled. However, our study is relatively consistent because both institutions have the same medical staff with the same principles.

Conclusions

In patients with lung cancer with MAO, palliative EBRT is effective and safe. High-dose irradiation (EQD2 ≥ 42.2 Gy) and prompt treatment (time to RT ≤ 14 days) may improve the response rate. Finding an optimal dose schedule, to reduce treatment duration and increase response while maintaining toxicity, should be investigated in future studies.

Abbreviations

MAO: malignant airway obstruction; EBRT: external beam radiotherapy; CT: computed tomography; GNUH: Gyeongsang National University Hospital; GNUCH: Gyeongsang National University Changwon Hospital; RT: radiotherapy; EQD2: equivalent dose in 2 Gy per fraction; PTV: planning target volume; ATS: American Thoracic Society; CR: complete response; PR: partial response; PD: progressive disease; SD: stable disease; RECIST: Response Evaluation Criteria In Solid Tumors; CTCAE: Common Terminology Criteria for Adverse Events; ECOG: Eastern Cooperative Oncology Group; OS: overall survival.

Declarations

Ethics approval and consent to participate

This study was retrospective, with no informed consent from individual patients, but was done in accordance with relevant guideline; the study protocol was approved by the Institutional Review Boards (IRBs) at GNUH (IRB No. GNUH 2020-03-009) and GNUCH (IRB No. GNUCH 2020-03-020).

Consent for publication

Not applicable because this analysis has retrospective nature

Availability of data and material

Raw data may be available on request from the corresponding author.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

Conception and design of the study: HSC, and KMK. Acquisition of data: HSC, BKJ, and IBH. Analysis and interpretation of the data: HSC, HJ, and KMK. Writing and revision of the manuscript: HSC, and KMK. All authors read and approved the final manuscript.

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Tables

Table 1. Patient characteristics

Variable		No. of patients	(%)
Age		Median 68 years	(range, 49-84years)
Sex	Male	60	80.0
	Female	15	20.0
Smoking history	Yes	66	88.0
	No	9	12.0
Comorbid COPD	Yes	16	21.3
	No	59	78.7
ECOG PS	0-1	38	50.7
	2	22	29.3
	3	15	20.0
Pathology	NSCLC	52	69.3
	SCLC	23	30.7
Disease status	Untreated	24	32.0
	Relapse or refractory	51	68.0
Degree of obstruction	Partial	56	74.7
	Total	19	25.3
Carina involvement	Yes	37	49.3
	No	38	50.7
Tumor length	< 5.6 cm	31	41.3
	≥ 5.6 cm	44	58.7
ATS score (before RT)	2	9	12.0
	3	32	42.7
	4	34	45.3

No., number; COPD, chronic obstructive pulmonary disease; ECOG, Eastern Cooperative Oncology Group; PS, performance status; NSCLC, non-small-cell lung cancer; SCLC, small-cell lung cancer; ATS, American Thoracic Society; RT, radiotherapy.

Table 2. Symptom changes before and after radiotherapy based on American thoracic society score

ATS score gap	No. of patients (%)	Symptom change
3	8 (10.7)	
2	18 (24)	Symptom improvement
1	20 (26.7)	(61.3%)
0	24 (32)	No change
-1 or -2	5 (6.7)	Symptom aggravation

ATS, American Thoracic Society; No., number.

Table 3. Prognostic factors for symptom improvement.

Univariate analysis			
Variable	Hazard ratio	95% CI	<i>p</i> value
ECOG PS (0-2 vs. 3)	12.08	2.29-63.59	0.003
DS status (untreated vs. relapse or refractory)	9.38	1.86-47.15	0.007
Degree of obstruction (partial vs. total)	0.15	0.04-0.61	0.008
Tumor length (< 5.6 cm vs. ≥ 5.6 cm)	33.25	3.94-280.44	0.001
EQD2 (< 42.2 Gy vs. ≥ 42.2 Gy)	0.19	0.06-0.65	0.007
Time to RT (≤ 14 days vs. > 14 days)	8.18	2.21-30.31	0.002
Tumor response (responding vs. non-responding)	51.33	5.98-441.03	< 0.001
Multivariate analysis			
Variable	Hazard ratio	95% CI	<i>p</i> value
EQD2 (< 42.2 Gy vs. ≥ 42.2 Gy)	13.92	4.94-158.92	0.034
Tumor response (responding vs. non-responding)	55.96	4.94-634.44	0.001

CI, confidence interval; ECOS, Eastern Cooperative Oncology Group; PS, performance status; vs., versus; DS, disease; EQD2, equivalent dose in 2 Gy per fraction; RT, radiotherapy.

Table 4. Prognostic factors for tumor response

Univariate analysis			
Variable	Hazard ratio	95% CI	<i>p</i> value
ECOG PS (0-2 vs. 3)	5.25	1.02-26.98	0.047
Pathology (NSCLC vs. SCLC)	0.21	0.05-0.91	0.036
DS status (untreated vs. relapse or refractory)	14.00	3.26-60.13	< 0.001
Degree of obstruction (partial vs. total)	0.28	0.09-0.91	0.034
EQD2 (< 42.2 Gy vs. ≥ 42.2 Gy)	0.21	0.06-0.72	0.013
Time to RT (≤ 14 days vs. > 14 days)	9.31	2.65-32.75	0.001
Multivariate analysis			
Variable	Hazard ratio	95% CI	<i>p</i> value
DS status (untreated vs. relapse or refractory)	10.71	1.97-58.31	0.006
EQD2 (< 42.2 Gy vs. ≥ 42.2 Gy)	0.13	0.02-0.77	0.024
Time to RT (≤ 14 days vs. > 14 days)	9.61	1.92-48.21	0.006

CI, confidence interval; ECOS, Eastern Cooperative Oncology Group; PS, performance status; vs., versus; NSCLC, non-small-cell lung cancer; SCLC, small-cell lung cancer; DS, disease; EQD2, equivalent dose in 2 Gy per fraction; RT, radiotherapy.

Figures

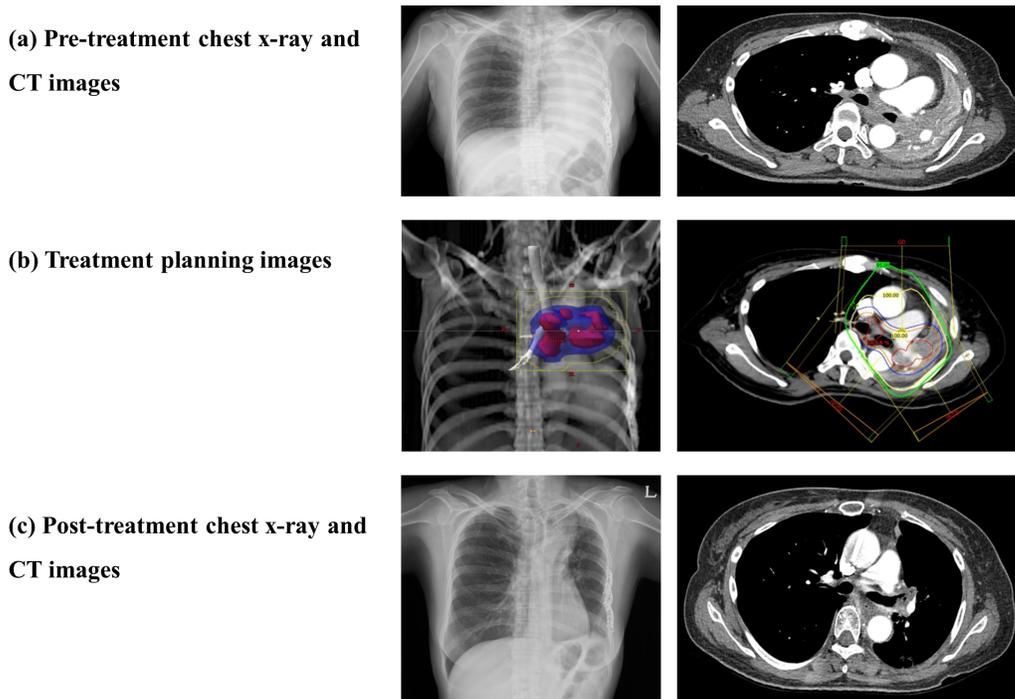


Figure 1

Images for a patient who underwent palliative radiotherapy for malignant airway obstruction. (a) Pre-treatment chest x-ray and CT images, (b) treatment planning images, and (c) post-treatment chest x-ray and CT images.

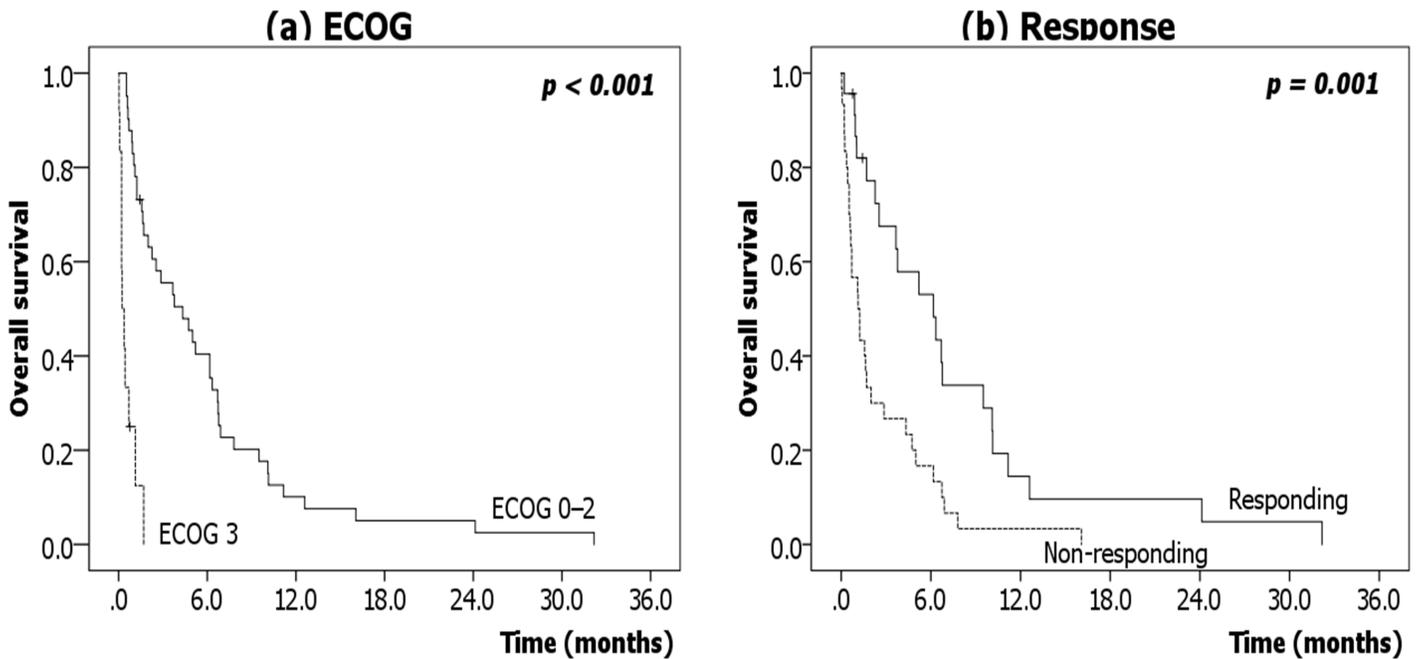


Figure 2

Overall survival according to (a) performance status and (b) tumor response.